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Predictive Factors of Rectal Toxicity after Permanent Iodine-125 Seed Implantation: Prospective Cohort Study in 2339 Patients

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Conflict of interest: none

ABSTRACT

Purpose: To evaluate the incidence and the associated factors of rectal toxicity in patients with prostate cancer undergoing permanent seed implantation (PI) with or without external beam radiation therapy (EBRT) in a nationwide prospective cohort study in Japan (J-POPS) during the first 2 years.

Methods and Materials: 2,339 subjects were available for the analyses. Rectal toxicity was evaluated using the NCI-CTCAE version 3.0.

Results: The 3-year cumulative incidence for Grade ≥2 rectal toxicity was 2.88%, 1.76% and 6.53% in all subjects, PI group and EBRT combination therapy group, respectively. On multivariate analysis, among all subjects, Grade ≥2 rectal toxicity was associated with rectal volumes receiving 100% of the prescribed dose (R100) (p <0.0001) and EBRT combination therapy (p = 0.0066). R100 in the PI group (p = 0.0254), and R100 (p = 0.0011) and interactive planning (p = 0.0267) in the EBRT combination therapy group were also associated with Grade ≥2 toxicity. The 3-year cumulative incidence of Grade ≥2 rectal toxicity was 3.80% and 1.37% for R100 ≥1 mL and R100 <1 mL, respectively in the PI group (p = 0.0068), and 14.09% and 5.52% for R100 ≥1 mL and R100 <1 mL, respectively in the EBRT combination therapy group (p = 0.0070).

Conclusions: Rectal toxicity was relatively rare in this study compared to previous reports. For Japanese prostate cancer patients, R100 <1 mL in both PI and EBRT combination therapy groups and interactive planning in EBRT combination therapy group may be effective in decreasing the incidence of rectal toxicity.

KEYWORDS: Prostate cancer, Brachytherapy, Rectal toxicity, External beam radiation therapy, Dose-volume histogram parameters, Interactive planning

INTRODUCTION

Permanent seed implantation (PI) has become a standard treatment option for patients with localized prostate cancer, with long-term local and biochemical control similar to outcomes observed after radical prostatectomy and external beam radiation therapy (EBRT) (1).

However, PI can lead to rectal toxicity, because the rectum, fixed in position and close to the prostate, often receives a large radiation dose with PI (2). Rectal toxicity is the third late effect of brachytherapy, after the urinary and sexual toxicity. Rectal toxicity of PI is variable in its presentation and can range in severity from mild, self-limited proctitis to more severe cases of ulceration and fistula formation (3–5).

The number of patients with prostate cancer treated with PI has increased rapidly in Japan, and over 19,000 patients had been treated in 109 institutions at the end of 2011 (6). To evaluate the safety and efficacy of PI for prostate cancer, a nationwide prospective cohort study entitled the Japanese Prostate Cancer Outcome Study of Permanent Iodine-125 (I-125) Seed Implantation (J-POPS; NCT00534196) was initiated in July 2005 (7). A total of 2,354 subjects were enrolled in the study during the first 2 years.

Ohashi *et al.* made the preliminary report evaluating the urinary and rectal toxicity in 2,339

subjects treated with PI enrolled in the J-POPS during the first 2 years (8). In this study, we describe rectal toxicity in more detail and evaluate factors associated with rectal toxicity in the same subjects.

METHODS AND MATERIALS

Although published previously (7, 8), a brief description of methods and materials are outlined below.

Patient eligibility

The J-POPS study is a large multi-institutional prospective cohort study to investigate the clinical effects of PI for localized prostate cancer in Japan (7). The enrollment of the subjects for this study has started in July 2005 and continued till December 2010. Finally 6,927 participants in 46 institutes had been registered and been followed up still now.

All subjects were histologically confirmed as having adenocarcinoma of the prostate and clinically diagnosed as having localized disease. There was no limitation for age, and all subjects gave written informed consent for enrollment in the J-POPS study. Inclusion and exclusion criteria of the participants followed the recommendations of the American Brachytherapy Society (9).

A total of 2,354 participants were enrolled in this study during the first 2 years. Out of 2,354 participants, background characteristics and baseline data were available in 2,339 patients.

Treatment design

All participants were treated with loose I-125 seeds. Modified peripheral loading or modified uniform loading was generally recommended for seed placement. The clinical target volume (CTV) was defined as the prostate volume including an added treatment margin of 3–5 mm in all directions, except for less than 2 mm in the posterior direction.

For PI alone as radiation therapy (PI group), a dose of 144 Gy was prescribed. According to the planning goals, V100 for the CTV (the percent volume of the CTV receiving 100% of the prescription dose) had to be over 90% or D90 for the CTV (the minimal dose received by 90% of the CTV) had to be 144–180 Gy. The maximum urethral dose had to be <200 Gy, whereas that for the rectum had to be <200 Gy in any slice.

For EBRT combination therapy (EBRT combination therapy group), the prescription dose for PI was 100–110 Gy and that for EBRT was 40–50 Gy with 1.8–2.0 Gy/fraction. As for EBRT, the target volume consisted of the prostate gland, seminal vesicles, small pelvis, and/or whole pelvis. EBRT was performed either before PI or approximately 1 month after PI. The maximum urethral and rectal dose for PI had to be <150% of the prescription dose. All the treatment techniques, such as 2-dimensional radiation therapy, 3-dimensional conformal radiation therapy, and intensity-modulated radiation therapy were allowed in this protocol.

Computed tomography (CT) images, taken at 1–3 mm slice width, were obtained approximately 1 month after PI for postimplant dosimetric evaluation. Dose-volume histograms (DVH) for the

prostate, urethra, and rectum were computed to obtain post-planning distribution data. The calculated dosimetry parameters were the percent volumes of the prostate receiving 100% and 150% of the prescribed dose (V100 and V150, respectively) and the values of the minimal dose received by 90% of the prostate volume (D90). The rectal dose was expressed as the rectal volume in cubic centimeters that received 100% and 150% of the prescribed dose (R100 and R150, respectively). The urethral dose was expressed as the values of the minimal dose received by 90% and 5% of the urethra volume (U-D90 and U-D5, respectively) and the urethral volume receiving 200% of the prescribed dose (U200).

Patient information is shown in Tables 1 and 2.

Toxicity scoring and follow-up protocol

The scheduled follow-up assessments involved prostate-specific antigen (PSA) blood tests and physical examinations every 3 months for the first 2 years, and every 6 months thereafter for 5 years. Toxicity was evaluated by physicians, mainly urologists, at 3, 12, 24, and 36 months after completion of radiation therapy.

The rectal toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 3.0, for proctitis and rectal bleeding (10). In this system, Grade 1 toxicity included mild adverse events (rectal discomfort or rectal bleeding that did not require intervention). Grade 2 toxicity included moderate adverse events (proctitis or rectal bleeding requiring medical intervention or minor cauterization). Grade 3 toxicity included severe

adverse events (proctitis requiring operative intervention or rectal bleeding requiring transfusion, interventional radiology, or endoscopic or operative intervention). Grade 4 toxicity included life-threatening or disabling adverse events (rectal perforation or rectal bleeding requiring major urgent intervention).

Acute toxicity was defined as symptoms occurring by 3 months after radiation therapy, and late toxicity was defined as symptoms occurring beyond 3 months after radiation therapy.

Statistical analysis

We estimated the cumulative incidence rate for Grade ≧2 rectal toxicity by the Kaplan Meier method to take into account of censored observations. We also identified the factors associated with Grade ≥2 rectal toxicity by the Cox proportional hazard model. Probability (p) values of <0.05 were defined to be significant. Multivariate analysis was performed to analyze factors that were found to be significantly associated with Grade ≥2 rectal toxicity in the univariate analysis.

Statistical analyses were performed by SAS 9.1.3 statistical software (SAS Institute Inc., Cary, NC, USA). All statistical analyses were carried out at the Translational Research Informatics Center (TRI) in the Foundation for Biochemical Research and Innovation (FBRI), a public interest incorporated foundation.

Ethical Considerations

The ethical review committee of the TRI (Approval no. 05-01; May 6, 2005) and all of the

institutional review boards of the participating facilities approved the study.

RESULTS

Incidence of acute and late rectal toxicity

The incidence of rectal toxicity was assessed at 3, 12, 24, and 36 months after completion of radiation therapy in 2,336, 2,310, 2,249, and 2,188 subjects, respectively.

The frequency of acute, late, and total rectal toxicity are shown in Table 3.

The 3-year cumulative incidence rate for Grade ≥2 rectal toxicity was 2.88% for all subjects, 1.76% for the PI group, and 6.53% for the EBRT combination therapy group (Fig. 1a). The 3-year cumulative incidence rate for Grade ≥2 proctitis was 1.57% for all subjects, 1.07% for the PI group, and 3.18% for the EBRT combination therapy group. The 3-year cumulative incidence rate for Grade ≥2 rectal bleeding was 1.71% for all subjects, 0.75% for the PI group, and 4.84% for the EBRT combination therapy group.

Only 3 subjects (0.55%; 3/547) in the EBRT combination therapy group experienced Grade 3 toxicity. Out of these 3 subjects, 2 had their symptoms resolved with argon plasma coagulation or hyperbaric oxygen therapy. One patient developed intractable bleeding and a rectourethral fistula, and a diverting colostomy was performed.

Factors associated with Grade ≥2 rectal toxicity

Tables 4, 5, and 6 show the results of the univariate and multivariate analyses using the Cox proportional hazard model for the effect of various factors on the incidence of Grade ≥2 rectal toxicity among all subjects, in the PI group, and in the EBRT combination therapy group, respectively.

On multivariate analysis, among all subjects, Grade ≥2 rectal toxicity was associated with rectal volumes receiving 100% of the prescribed dose (R100) (hazard ratio [HR], 1.885; 95% confidence interval [CI], 1.383–2.569; p <0.0001) and EBRT combination therapy (HR, 2.815; 95% CI, 1.334–5.939; p = 0.0066). R100 in the PI group (HR, 1.655; 95% CI, 1.064–2.574; p = 0.0254), and R100 (HR, 1.977; 95% CI, 1.314–2.974; p = 0.0011) and interactive planning (HR, 0.472; 95% CI, 0.243–0.917; p = 0.0267) in the EBRT combination therapy group was also associated with Grade ≥2 toxicity.

In the PI group, the 3-year cumulative incidence rate of Grade ≥2 rectal toxicity exceeded 3% with R100 ≥ 1 mL; 3.80% for R100 ≥ 1 mL, and 1.37% for R100 < 1 mL (HR, 2.757; 95% CI, 1.282–5.929; p = 0.0068) (Fig. 1b). In the EBRT combination therapy group, the 3-year cumulative incidence rate of Grade ≥2 rectal toxicity exceeded 10% with R100 ≥ 1 mL; 14.09% for R100 ≥ 1 mL, and 5.52% for R100 < 1 mL (HR, 2.744; 95% CI, 1.286–5.857; p = 0.0070) (Fig. 1c). In the EBRT combination therapy group, the 3-year cumulative incidence rate of Grade ≥2 rectal toxicity was 4.87% for interactive planning and 10.25% for other plannings (Fig. 1d).

DISCUSSION

Rectal toxicity is the third late effect of brachytherapy, after the urinary and sexual toxicity, and many publications have described the incidence and severity of rectal toxicity after PI (3, 5, 11–15). However, no reports have included more than 1,000 patients and been prospectively designed. To our knowledge, this is the largest prospective report of rectal toxicity after PI.

Grade ≥2 rectal toxicity is reported to occur in 2.0–10.4% of patients treated with PI (5, 11–16) and in 8.0–18.0% of patients treated with EBRT combination therapy (11, 15–17). In our study, the 3-year cumulative incidence rate of Grade ≥2 rectal toxicity was 1.76% for the PI group and 6.53% for the EBRT combination therapy group. These findings were relatively favorable results as compared to other studies. We assume that this is largely attributable to the rectal dose being lower than those in other studies. The mean and median R100 in all patients was 0.48 mL and 0.30 mL in our study, whereas other studies have reported a mean or median R100 of 0.79–1.49 mL (5, 11, 18, 19). This might be explained by the superior quality of the technique used at these institutions. Training workshops have been held at regular intervals in Japan to maintain or improve the technical level of PI (6), and all the institutions in this study have participated the workshops. In each institution, PI treatment was performed with the strict aim of sparing the rectum. Additionally, a smaller prostate volume (PV) might result in a lower rectal dose. McNeely *et al*. (20) and Patil *et al*. (19) reported that the rectal dose increased in tandem with an enlarging PV. The mean and median PV in all subjects was 25.90 mL and 25.19 mL in our study, whereas the aforementioned studies have reported a mean or median PV of 28.0–38.5 mL (5, 11, 18, 19).

Factors reportedly associated with rectal toxicity in PI include the addition of EBRT (15, 17, 21–24), rectal dose (3, 11, 13–15, 25), prostate dose (15, 26, 27), advanced age (22, 21), inflammatory bowel disease (22), and smoking status (21). Prostate volume (19, 20) and body mass index (19) were reported to be associated with the rectal dose in PI. Diabetes mellitus, prior abdominal surgery, and androgen deprivation therapy were reported to be associated with rectal toxicity in EBRT (28). We performed this study on the basis of the hypothesis that these factors might be associated with rectal toxicity. Indeed, when we analyzed all 2,339 cases, Grade ≥2 rectal toxicity was associated with R100 and the addition of EBRT. R100 in the PI group and R100 and interactive planning in the EBRT combination therapy group were also associated with Grade ≥2 rectal toxicity. With regard to the planning process, several investigators have reported that DVH parameters are significantly better with intraoperative planning than preplanning (29). Zelefsky *et al.* (30) reported a more rapid resolution of Grade 2 urinary-related symptoms with interactive planning than preplanning. However, prior to our study, no reports have demonstrated that rectal toxicity was rarer with intraoperative planning than preplanning.

In this study, the 3-year cumulative incidence rate of Grade ≥2 rectal toxicity was 3.80% for R100 ≥1 mL and 1.37% for R100 <1 mL, respectively, in the PI group (HR, 2.757; 95% CI, 1.282–5.929; $p = 0.009$), and 14.09% for R100 ≥1 mL and 5.52% for R100 <1 mL, respectively, in the EBRT combination therapy group (HR, 2.744; 95% CI, 1.286–5.857; $p = 0.009$). Snyder *et al.* (13) have shown that Grade ≥2 proctitis at 5 years was seen in 18% of patients with R100 >1.3 mL and in 5% of patients with R100 ≤1.3 mL among patients receiving PI ($p = 0.001$). Keyes *et al.* (5) have

shown that, for PI, late Grade ≥2 rectal toxicity was seen in 10.6% of patients with R100 ≥1 mL and in 6.7% of patients with R100 ≤1 mL. Shiraishi *et al.* (31) have shown that, for EBRT combination therapy, Grade 2 rectal bleeding was seen in 22.0% of patients with R100 >1 mL and in 8.1% of patients with R100 ≤1 mL. Keyes *et al.* (5), Tran *et al.* (32), and Han *et al.* (33) suggested keeping R100 <1 mL. These reports are consistent with our data in terms of association of R100 with rectal toxicity.

This study has some limitations. First, interobserver variability in postimplant dosimetry exists because this study was a multicenter study. Contouring the prostate and rectum on postimplant CT images can be challenging (34). However, because the above-mentioned training workshops in which all the institutions in this study have participated include the technical instruction of postimplant dosimetry, interobserver variability in this study should be minimized. Secondly, we did not analyze the rectal DVH parameters for EBRT in the EBRT combination therapy group, although Shiraishi *et al.* (31) reported that rectal V30 (the percent volumes receiving doses higher than 30 Gy) for EBRT was associated with Grade 2 rectal bleeding in patients receiving EBRT combination therapy and rectal DVH parameters were reported to be associated with rectal toxicity in patients receiving EBRT (28). Finally, the follow-up period may be too short to observe late rectal toxicity. The final follow-up of toxicity was at 36 months in our protocol, although rectal toxicity could appear after more than 3 years.

CONCLUSIONS

Rectal toxicity after PI with and without EBRT was relatively rare in our study as compared to previous reports. For Japanese patients with prostate cancer treated with PI, R100 <1 mL both in PI and EBRT combination therapy and interactive planning in EBRT combination therapy may be effective in decreasing the incidence of rectal toxicity.

FIGURE CAPTIONS

Fig. 1. (a) Cumulative Grade ≥2 rectal toxicity rates for the PI group and the EBRT combination therapy group. (b) Cumulative Grade ≥2 rectal toxicity rates for R100 ≥ 1 mL and R100 < 1 mL in the PI group. (c) Cumulative Grade ≥2 rectal toxicity rates for R100 ≥ 1 mL and R100 < 1 mL in the EBRT combination therapy group. (d) Cumulative Grade ≥2 rectal toxicity rates for interactive planning and other plannings in the EBRT combination therapy group.

PI = permanent seed implantation; EBRT = external beam radiation therapy; R100 = the rectal volume in cubic centimeters that receiving 100% of the prescribed dose.

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Table 1 Descriptive statistics of patient information

Factors	n	mean	SD	minimum	median	maximum	missing
Age (year)	2339	68.07	6.37	45	69.0	89	0
PI group	1792	67.81	6.47	45	68.5	89	0
EBRT combination group	547	68.92	5.98	52	70.0	88	0
BMI (kg/m^2)	2268	23.60	2.67	14.69	23.51	35.70	71
PI group	1721	23.63	2.62	14.69	23.57	32.78	71
EBRT combination group	547	23.50	2.83	15.50	23.38	35.70	0
PSA (ng/ml) *	2321	7.98	4.10	1.60	6.80	42.00	18
PI group	1775	7.19	3.11	1.60	6.47	41.80	17
EBRT combination group	546	10.57	5.60	1.92	9.33	42.00	1
Prostate volume (ml) †	2339	25.90	8.23	7.00	25.19	71.00	0
PI group	1792	26.40	8.17	7.30	25.75	71.00	0
EBRT combination group	547	24.25	8.22	7.00	23.53	61.90	0
Implanted seed number	2339	68.26	16.55	25	69.0	120	0
PI group	1792	73.26	14.74	26	73.0	120	0
EBRT combination group	547	51.87	10.42	25	50.0	85	0
Activity/seed (MBq)	2339	13.39	1.01	9.79	13.10	15.30	0
PI group	1792	13.38	0.95	9.79	13.10	15.30	0
EBRT combination group	547	13.41	1.20	10.62	13.10	15.30	0
Total activity (MBq)	2339	912.13	225.09	332.50	917.00	1572.00	0
PI group	1792	978.44	201.50	340.60	969.40	1572.00	0
EBRT combination group	547	694.91	148.55	332.50	679.32	1224.00	0
Prostate V100 (%)	2327	93.89	5.23	56.30	95.13	100.00	12
PI group	1781	93.66	5.19	56.30	94.80	100.00	11
EBRT combination group	546	94.62	5.30	56.47	96.07	99.97	1
Prostate V150 (%)	2327	62.38	13.51	16.32	63.32	98.10	12
PI group	1781	62.16	13.45	18.42	62.94	94.60	11
EBRT combination group	546	63.08	13.69	16.32	64.21	98.10	1

Prostate D90 (Gy)	2327	151.20	27.40	57.80	152.36	231.90	12
PI group	1781	160.87	22.71	57.80	160.60	231.90	11
EBRT combination group	546	119.67	14.78	60.22	120.40	191.60	1
R100 (ml)	2231	0.48	0.58	0.00	0.30	4.78	108
PI group	1685	0.50	0.59	0.00	0.30	4.78	107
EBRT combination group	546	0.43	0.53	0.00	0.26	3.73	1
R150 (ml)	2231	0.05	0.13	0.00	0.00	1.51	108
PI group	1685	0.05	0.13	0.00	0.00	1.51	107
EBRT combination group	546	0.04	0.11	0.00	0.00	1.21	1
Urethral D90 (Gy)	2230	133.24	32.71	7.90	131.55	336.54	109
PI group	1684	140.70	32.53	7.90	140.43	336.54	108
EBRT combination group	546	110.24	20.16	40.00	110.68	184.73	1
Urethral D5 (Gy)	1996	212.08	46.96	97.60	210.00	426.99	343
PI group	1479	227.26	41.03	119.00	223.39	426.99	313
EBRT combination group	517	168.66	34.01	97.60	161.99	338.36	30
U200 (ml)	2230	0.06	1.97	0.00	0.00	92.90	109
PI group	1684	0.07	2.27	0.00	0.00	92.90	108
EBRT combination group	546	0.01	0.05	0.00	0.00	0.60	1

SD = standard deviation; PI = permanent seed implantation; EBRT = external beam radiation therapy; BMI = body mass index; PSA = prostate-specific antigen; VXX = the percent volumes receiving XX% of the prescribed dose; DXX = the values of the minimal dose received by XX% of the volume; RXX = the rectal volume in cubic centimeters that receiving XX% of the prescribed dose; U200 = the urethral volume receiving 200% of the prescribed dose

*PSA was measured before the latest biopsy.

†Prostate volume was measured pre-implantation.

Table 2 Baseline characteristics of patients

Factors	PI group		EBRT combination group		Total	
	n	%	n	%	n	%
Diabetes						
Yes	113	6.31	44	8.04	157	6.72
No	1678	93.69	503	91.96	2181	93.28
Rectal cancer						
Yes	12	0.67	5	0.91	17	0.73
No	1779	99.33	542	99.09	2321	99.27
Bladder cancer						
Yes	10	0.56	6	1.10	16	0.68
No	1781	99.44	541	98.90	2322	99.32
Smoking status						
Yes	239	14.60	74	13.83	313	14.41
No	1398	85.40	461	86.17	1859	85.59
Drinking status						
Yes	1111	68.03	394	73.78	1505	69.45
No	522	31.97	140	26.22	662	30.55
Gleason score						
8 or more	12	0.67	72	13.16	84	3.60
7	545	30.46	384	70.20	929	39.77
6 or less	1232	68.87	91	16.64	1323	56.64
Clinical stage: T Stage						
T3	2	0.11	16	2.93	18	0.77
T2	394	22.02	207	37.84	601	25.73
T1	1388	77.59	324	59.23	1712	73.29
TX	5	0.28	-	-	5	0.21
Clinical stage: N Stage						
N0	1776	99.27	546	99.82	2322	99.40
NX	13	0.73	1	0.18	14	0.60
Clinical stage: M Stage						
M0	1774	99.16	546	99.82	2320	99.32
MX	15	0.84	1	0.18	16	0.68
Androgen deprivation therapy						
Yes	764	42.63	390	71.30	1154	49.34
No	1028	57.37	157	28.70	1185	50.66
Planning process						
Interactive	772	43.08	374	68.37	1146	49.00
Others	1020	56.92	173	31.63	1193	51.00

Table 3 Crude frequency of rectal toxicities

	PI group						EBRT combination group						All patients					
	Acute		Late		Total		Acute		Late		Total		Acute		Late		Total	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Grade4	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Grade3	0	0.00	0	0.00	0	0.00	0	0.00	3	0.56	3	0.55	0	0.00	3	0.13	3	0.13
Grade2	15	0.84	16	0.90	31	1.73	9	1.65	24	4.45	32	5.85	24	1.03	40	1.72	63	2.69
Grade1	117	6.54	132	7.45	209	11.67	50	9.16	109	20.22	125	22.85	167	7.15	241	10.42	334	14.29
Grade0	1658	92.63	1625	91.65	1551	86.60	487	89.19	403	74.77	387	70.75	2145	91.82	2028	87.72	1938	82.89
Total	1790	100.00	1773	100.00	1791*	100.00	546	100.00	539	100.00	547	100.00	2336	100.0	2312	100.00	2338*	100.00

PI = permanent seed implantation; EBRT = external beam radiation therapy.

* One patient was missing due to loss to follow up.

Table 4 Univariate and multivariate analyses for Grade ≥2 rectal toxicity among all patients

Factors		Univariate analysis				Multivariate analysis			
		n	HR	95% CI	*p*	n	HR	95% CI	*p*
Age (years)		2339	1.019	0.980–1.059	0.3501				
BMI (kg/m^2)		2268	0.956	0.871–1.049	0.3414				
Prostate volume (ml)		2339	0.981	0.951–1.012	0.2226				
Activity/seed (MBq)		2339	0.999	0.786–1.268	0.9920				
Prostate V100 (%)		2327	0.972	0.934–1.012	0.1638				
Prostate V150 (%)		2327	1.016	0.997–1.035	0.1014				
Prostate D90 (Gy)		2327	0.983	0.974–0.991	0.0001*	2226	0.992	0.979–1.006	0.2637
R100 (ml)		2231	1.701	1.259–2.297	0.0005*	2226	1.885	1.383–2.569	<.0001*
R150 (ml)†		2231	7.418	2.862–19.223	<.0001*				
Diabetes	Yes	157	1.396	0.603–3.232	0.4355				
	No	2181							
Rectal cancer	Yes	17	2.186	0.303–15.753	0.4377				
	No	2321							
Smoking status	Yes	313	1.355	0.724–2.535	0.3421				
	No	1859							
Drinking status	Yes	1505	1.065	0.624–1.817	0.8176				
	No	662							
Clinical stage	T1	1712				1637			
	T2	601	1.684	1.018–2.787	0.0425	571	1.360	0.811–2.282	0.2439
	T3	18	—	—	0.9839	18	0.000	0.000	0.9854
Androgen deprivation therapy	Yes	1154	1.283	0.762–2.009	0.3886				
	No	1185							
EBRT	Yes	547	3.766	2.322–6.107	<.0001*	546	2.815	1.334–5.939	0.0066*
	No	1792				1680			
Planning process	Interactive	1146	1.160	0.715–1.881	0.5470				
	Other	1193							

HR = hazard ratio; CI = confidence interval; Other abbreviations as in Table 1.

*: Significant risk factor

†: R150 is the collinearity factor of R100; therefore, R150 is excluded in the multivariate analysis.

One patient was treated but lacked the data for the rectal toxicity; as a censored sample the patient was included for the calculation of HR. Therefore, total n=2339 if explanatory variables were measured for all the patients.

Table 5 Univariate and multivariate analyses for Grade ≥2 rectal toxicity in the PI monotherapy group

Factors		Univariate analysis				Multivariate analysis			
		n	HR	95% CI	*p*	n	HR	95% CI	*p*
Age (years)		1792	0.991	0.939–1.046	0.7443				
BMI (kg/m^2)		1721	0.971	0.846–1.114	0.6715				
Prostate volume (ml)		1792	0.964	0.919–1.010	0.1205				
Activity/seed (MBq)		1792	1.077	0.751–1.546	0.6860				
Prostate V100 (%)		1781	0.953	0.903–1.006	0.0805				
Prostate V150 (%)		1781	1.008	0.982–1.036	0.5441				
Prostate D90 (Gy)		1781	0.997	0.981–1.012	0.6798				
R100 (ml)		1685	1.655	1.064–2.574	0.0254*	1685	1.655	1.064–2.574	0.0254*
R150 (ml)†		1685	5.459	1.167–25.539	0.0311*				
Diabetes	Yes	113	2.224	0.778–6.355	0.1356				
	No	1678							
Rectal cancer	Yes	12	—	—	0.9894				
	No	1779							
Smoking status	Yes	239	1.795	0.770–4.183	0.1754				
	No	1398							
Drinking status	Yes	1111	1.096	0.502–2.393	0.8184				
	No	522							
Clinical stage	T1	1388							
	T2	394	1.522	0.697–3.323	0.2917				
	T3	2	—	—	0.9902				
Androgen deprivation therapy	Yes	764	1.109	0.547–2.249	0.7747				
	No	1028							
Planning process	Interactive	772	1.590	0.784–3.225	0.1990				
	Other	1020							

Abbreviations as in Table 4.

*: Significant risk factor

†: R150 is the collinearity factor of R100; therefore, R150 is excluded in the multivariate analysis.

One patient was treated but lacked the data for the rectal toxicity; as a censored sample the patient was included for the calculation of HR. Therefore, total n=1792 if explanatory variables were measured for all the patients.

Table 6 Univariate and multivariate analyses for Grade ≥2 rectal toxicity in the EBRT combination therapy group

Factors		Univariate analysis				Multivariate analysis			
		n	HR	95% CI	*p*	n	HR	95% CI	*p*
Age (years)		547	1.032	0.976–1.092	0.2621				
BMI (kg/m^2)		547	0.956	0.846–1.081	0.4726				
Prostate volume (ml)		547	1.014	0.975–1.054	0.4867				
Activity/seed (MBq)		547	0.943	0.712–1.250	0.6847				
Prostate V100 (%)		546	0.977	0.926–1.030	0.3872				
Prostate V150 (%)		546	1.019	0.994–1.046	0.1423				
Prostate D90 (Gy)		546	1.003	0.981–1.026	0.8029				
R100 (ml)		546	2.026	1.332–3.082	0.0010*	546	1.977	1.314–2.974	0.0011*
R150 (ml)†		546	14.320	4.247–48.288	<.0001*				
Diabetes	Yes	44	0.678	0.163–2.824	0.5932				
	No	503							
Rectal cancer	Yes	5	3.177	0.435–23.212	0.2546				
	No	542							
Smoking status	Yes	74	1.038	0.403–2.676	0.9377				
	No	461							
Drinking status	Yes	394	0.885	0.425–1.844	0.7450				
	No	140							
Clinical stage	T1	324							
	T2	207	1.176	0.602–2.297	0.6351				
	T3	16	—	—	0.9899				
Androgen deprivation therapy	Yes	390	0.682	0.344–1.354	0.2864				
	No	157							
Planning process	Interactive	374	0.469	0.242–0.911	0.0254*	374	0.472	0.243–0.917	0.0267*
	Other	173				172			

Abbreviations as in Table 4.

*: Significant risk factor

†: R150 is the collinearity factor of R100; therefore, R150 is excluded in the multivariate analysis.

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